Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years

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Objective: To evaluate the efficacy of annual mammography over and above annual physical examination of the breasts and the teaching of breast self-examination among women aged 50 to 59 on entry.

Design: Individually randomized controlled trial.

Setting: Fifteen urban centres in Canada with expertise in the diagnosis and treatment of breast cancer.

Participants: Women with no history of breast cancer and no mammography in the previous 12 months were randomly assigned to undergo either annual mammography and physical examination (MP group) or annual physical examination only (PO group). The 39 405 women enrolled from January 1980 through March 1985 were followed for a mean of 8.3 years.

Data collection: Derived from the participants by initial and annual self-administered questionnaires, from the screening examinations, from the patients' physicians, from the provincial cancer registries and by record linkage to the Canadian National Mortality Data Base. Expert panels evaluated histologic and death data.

Main outcome measures: Rates of referral from screening, rates of detection of breast cancer from screening and from community care, nodal status, tumour size and rates of death from all causes and from breast cancer.

Results: Over 85% of the women in each group attended the screening sessions after screen 1. The characteristics of the women in the two groups were similar. Compared with the Canadian population the participants were more likely to be married, have fewer children, have more education, be in a professional occupation, smoke less and have been born in North America. The rate of screen-detected breast cancer on first examination was 7.20 per 1000 in the MP group and 3.45 per 1000 in the PO group; more node-positive tumours were found in the MP group than in the PO group. At subsequent screens the detection rates were a little less than half the rates at screen 1. During years 2 through 5 the ratios of observed to expected cases of invasive breast cancer were 1.28 in the MP group and 1.18 in the PO group. Of the women with

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invasive breast cancer through to 7 years, 217 in the MP group and 184 in the PO group had no node involvement, 66 and 56 had one to three nodes involved, 32 and 34 had four or more nodes involved, and 55 and 46 had an unknown nodal status. There were 38 deaths from breast cancer in the MP group and 39 in the PO group. The ratio of the proportions of death from breast cancer in the MP group compared with those in the UC group was 0.97 (95% confidence interval 0.62 to 1.52). The survival rates were similar in the two groups. Women whose cancer had been detected by mammography alone had the highest survival rate.

Conclusion: The study was internally valid, and there was no evidence of randomization bias. Screening with yearly mammography in addition to physical examination of the breasts detected considerably more node-negative, small tumours than screening with physical examination alone, but it had no impact on the rate of death from breast cancer up to 7 years' follow-up from entry.

Objectif : Évaluer l'efficacité de la mammographie annuelle en plus de l'examen physique annuel des seins et de l'enseignement de l'auto-examen des seins chez les femmes de 50 à 59 ans à l'entrée.

Conception : Étude aléatoire contrôlée individuelle.

Cadre : Quinze centres urbains au Canada possédant une compétence en diagnostic et traitement du cancer du sein.

Participantes : Nous avons choisi au hasard des femmes sans antécédents de cancer du sein et n'ayant pas subi de mammographie dans les 12 mois précédents afin qu'elles passent soit une mammographie annuelle avec examen physique (groupe MP) ou uniquement un examen physique annuel (groupe PO). Les 39 405 femmes inscrites de janvier 1980 à mars 1985 ont été suivies 8,3 ans en moyenne.

Collection des données : Données obtenues des participantes grâce au questionnaire d'entrée, aux questionnaires annuels autoadministrés et aux examens de dépistage et par l'entremise des médecins traitants, des registres provinciaux de cancérologie et en établissant un lien entre le dossier et la base de données nationale sur la mortalité au Canada. Les données histologiques et de décès ont été évaluées par des groupes de spécialistes.

Principales mesures des résultats : Taux de consultations découlant du dépistage, taux de détection du cancer du sein par dépistage et par les soins de santé communautaire, état ganglionnaire, taille de la tumeur et taux de décès de toutes causes et par cancer du sein.

Résultats : Plus de 85 % des femmes de chaque groupe ont assisté aux séances de dépistage de la 2e à la 5e année. Dans les deux groupes, les caractéristiques des femmes étaient analogues. Comparativement à la population canadienne, les participantes étaient plus susceptibles d'être mariées, d'avoir moins d'enfants, d'être plus scolarisées, d'occuper une situation professionnelle, de moins fumer et d'être nées en Amérique du Nord. Le taux de cancers décelés par dépistage au premier examen était de 7,20 par 1 000 dans le groupe MP et de 3,45 par 1 000 dans le groupe PO; nous avons observé un plus grand nombre de tumeurs à atteinte ganglionnaire dans le groupe MP que dans le groupe PO. Aux examens subséquents, les taux de dépistage étaient légèrement inférieurs à la moitié des taux du premier examen. De la 2e à la 5e année, les ratios entre les cas observés et prévus de cancers envahissants du sein étaient de 1,28 dans le groupe MP et de 1,18 dans le groupe PO. Parmi les femmes atteintes d'un cancer envahissant du sein au cours des 7 années, 217 du groupe MP et 184 du groupe PO ne présentaient aucune atteinte ganglionnaire, 66 et 56 respectivement présentaient d'un à trois ganglions atteints, 32 et 34, au moins quatre ganglions atteints, tandis que pour 55 et 46 l'état ganglionnaire était inconnu. Il y a eu 38 décès par cancer du sein dans le groupe MP et 39 dans le groupe PO. Le ratio des proportions de décès par cancer du sein dans le groupe MP comparativement au taux dans le groupe PO était de 0,97 (intervalle de confiance de 95 %, 0,62 à 1,52). Les taux de survie étaient analogues dans les deux groupes. Le taux de survie était le plus élevé chez les femmes dont le cancer avait été dépisté par la mammographie uniquement.

Conclusion : L'étude était valide sur le plan interne et nous n'avons relevé aucune preuve de gauchissement aléatoire. Le dépistage par la mammographie annuelle en plus de l'examen physique des seins a permis de déceler beaucoup plus de petites tumeurs sans atteinte ganglionnaire que le dépistage par examen physique uniquement, mais n'a eu aucune effet sur le taux de décès par cancer du sein jusqu'à 7 années de suivi à partir de l'entrée.

Part 2 of the Canadian National Breast Screening Study (NBSS) is an individually randomized trial designed to evaluate the efficacy of annual mammography over and above annual physical examination of the breasts and the teaching of breast self-examination in reducing the rate of death from breast cancer among women aged 50 to 59 years on entry.[1]

Screening for breast cancer among women aged 50 or more with mammography, alone or in combination with physical examination of the breasts, has been found to be effective in reducing the rate of death from breast cancer.[2] However, it is unclear how much mammography contributes to this over and above any benefit from physical examination alone. The Working Group to Review the National Cancer Institute–American Cancer Society Breast Cancer Detection Demonstration Projects recommended that a trial be conducted to examine this issue.[3] The NBSS was designed to meet this need.

In this article we present the findings from the first 7 years of follow-up for women aged 50 to 59 years on entry to the NBSS. Part 1 of the NBSS, reported in the accompanying paper (see pages 1459 to 1476 of this issue), evaluated the efficacy of the combination of annual mammography, physical examination of the breasts and the teaching of breast self-examination in reducing the rate of death from breast cancer among women aged 40 to 49 years on entry to the study. Reports on some aspects of the study have appeared, including those on the early phase of recruitment,[4] changes in breast self-examination behaviour,[5] the sensitivity of the screening methods[6–8] and the early results.[9,10]

Methods

Full details of the methods of the NBSS are given in the accompanying paper (see pages 1461 to 1465).

Given the rate of death from breast cancer in Canada among women aged 50 to 59, to detect a 40% reduction in the death rate the total sample would have to be 40 000 women, at an α level of 0.05 and a power of 80% after 5 years of follow-up.[1] In practice, the number of deaths from breast cancer at 5 years was insufficient to achieve the planned power. Therefore, the follow-up was extended for 2 years.

The recruitment and randomization processes were the same as those in part 1. The only difference in the eligibility criteria, which were described in detail elsewhere,[1] was age (50 to 59 years).

Participants were randomly assigned to undergo either annual mammography and physical examination (MP group) or annual physical examination only (PO group). The first 62% of the women who entered the study were offered five annual screening examinations and the remainder four. Breast self-examination was taught at the initial examination and the teaching reinforced at subsequent examinations. The screening procedures were the same as those outlined in the accompanying paper.

The follow-up procedure, the ascertainment of deaths and the verification of causes of death were as described in part 1.

The NBSS database includes records of 39 476 women aged 50 to 59 entered in the study from January 1980 through March 1985. Quality control and collection of data were the same as described in part 1, as was the determination of tumour size and node involvement.

For definitions of the NBSS terminology and a description of the methods of analysis see pages 1464 and 1465 of part 1.

Of the 39 476 women who entered the study 71, distributed equally between the two groups, were excluded from the analysis for the following reasons: (a) lost files (files for 7 participants were permanently mislaid), (b) total refusal (32 participants withdrew from the study after group assignment and demanded to have their study records destroyed), (c) wrong screening procedure (22 women did not undergo mammography and should have or vice versa), (d) wrong age (6 women were more than 59 years at entry) and (e) recent mammography (4 women had undergone mammography within the year before joining the study).

The protocol violations judged not to require exclusion from the study were as follows: (a) double assignment (in 19 cases two women were given the same identification number) and (b) wrong age list (162 women were on the wrong list because of an error in calculating their age from the birth date on the questionnaire).

Data are presented in the manner described in part 1 (see page 1465).

Results

The active recruitment phase lasted from January 1980 to the end of March 1985. Of the 39 405 women enrolled in the study 6% were recruited in 1980, 14% in 1981, 16% in 1982, 21% in 1983, 34% in 1984 and 9% in 1985. Screening continued until June 1988. The follow-up period ranged from 5.3 to 12 (mean 8.3) years.

Characteristics of the study population

Detailed analyses of the epidemiologic variables reported on the questionnaire were performed by centre and province. An analysis by single year of

age indicated almost an equal distribution between the two groups.

Table 1 summarizes the data for other epidemiologic variables by group. The last column gives the data for the Canadian population matched for age and sex.[11]

Differences between the two groups were minimal, being less than 1% for a given characteristic in most instances. In addition to the data presented in Table 1, there were minimal differences in oral estrogen use.

Compared with the Canadian population fewer participants were widowed, more had no or one to four children and fewer had six or more children. Substantially more had trade or business training or a university education. More had been born in North America and fewer in Europe or elsewhere. Slightly fewer had never smoked, even fewer were heavy smokers, and twice as many were former smokers. More worked in clerical, health-related, teaching, managerial or administrative, science-related or technology-related occupations, with correspondingly fewer in sales and service and "other" occupations.

Compliance with screening

In the MP group full compliance with screening after screen 1 (when, by definition, compliance was 100%) varied from 86.7% (for screen 5) to 90.4% (for screen 2). In addition, a small proportion (1.8% to 3.2%) of the women accepted physical examination but refused to undergo mammography. Of the women in the MP group 2.8% to 7.0% missed one or more screens after screen 1 but still submitted questionnaires. In the PO group compliance with the annual screening varied between 89.1% (for screen 2) and 85.4% (for screen 5); questionnaires only were obtained for 2.8% to 7.0% of the women.

Referral to review clinic

Table 2 displays the reasons for referral to the NBSS review clinic. Referrals were more frequent in the MP group than in the PO group because of mammographic abnormalities detected in the absence of physical findings. In the two groups the proportion of women referred decreased after screen 1. The contribution of physical findings to the referral rate was almost equal in the two groups at each screening.

Impact of recommendations from the screening centres

Table 3 gives the diagnostic procedures recommended by the study surgeons and the procedures actually performed. In general, more procedures were recommended and performed in the MP group than in the PO group, and more were performed at screen 1 than at subsequent screens. Diagnostic mammography in the community was sometimes recommended by the study surgeon, more frequently for women in the PO group than for those in the MP group. Less diagnostic mammography was performed than recommended. In the MP group NBSS mammograms were often used in the community for diagnostic purposes.

Mammography was also performed in the community and was reported by participants on the annual questionnaires. In some cases the mammography was ordered to investigate abnormalities detected between screening examinations. The numbers of women reporting community mammography once or more during the study period were 1196 (6.1%) of those in the MP group and 3330 (16.9%) of those in the PO group. The proportion in the MP group remained stable across the screening years, ranging between 1.9% and 2.2%. In contrast, the proportion increased slightly over time in the PO group, from 5.3% between years 1 and 2 to 8.0% between years 4 and 5.

Table 4 shows the benign biopsy rates; only surgical biopsies, with or without needle localization, were included. The rate in the PO group reflected the North American experience.[12] The higher rates in the MP group reflected the use of biopsy in community institutions as the definitive diagnostic test. The rates were particularly high in the MP group and at screen 1.

Cancer detection rates

The rates of screen-detected cancer, including in-situ and invasive cancer, are shown in Table 5 by year of screening examination. Women who did not return after screen 1 were not included in the denominators for screens 2 through 5. Overall the detection rate was higher in the MP group than in the PO group; in both groups the rates were higher at screen 1 than at other times. At screen 1 the rate of detection by physical examination was higher in the MP group (alone or in combination with mammography) than in the PO group (alone) (3.90 v. 3.45 per 1000); this difference was not statistically significant.

The rates of interval cancer are presented in Table 5. The denominator was the number of women in the same group who had attended the previous screen. The rate was higher in the PO group than in the MP group throughout the screening period (by 6% at interval 1, by 38% at interval 2, by 70% at interval 3, by 45% at interval 4 and by 69% at interval 5). These differences suggest that the addi-

Table 1: Demographic characteristics of women aged 50 to 59 years upon entry into the Canadian National Breast Screening Study (NBSS) and women in the general population

Characteristic	Study group;* no. (and %) of women: MP group (n = 19 711)	PO group (n = 19 694)	% of women in Canada
Marital status	(n = 19 684)	(n = 19 655)	
Never married	1 184 (6.0)	1 243 (6.3)	6.6
Married	15 554 (79.0)	15 438 (78.5)	75.5
Separated or divorced	1 653 (8.4)	1 593 (8.1)	7.7
Widowed	1 293 (6.6)	1 381 (7.0)	10.3
No. of live births†	(n = 18 429)	(n = 18 338)	
0	1 696 (9.2)	1 662 (9.1)	9.2
1	1 598 (8.7)	1 557 (8.5)	10.5
2	4 231 (23.0)	4 349 (23.7)	21.6
3	4 714 (25.6)	4 638 (25.3)	20.5
4	3 138 (17.0)	3 070 (16.7)	14.8
5	1 561 (8.5)	1 543 (8.4)	8.8
≥ 6	1 491 (8.1)	1 519 (8.3)	14.6
Reproductive status	(n = 19 711)	(n = 19 694)	
Premenopausal	2 653 (13.5)	2 736 (13.9)	–
Perimenopausal	440 (2.2)	447 (2.3)	–
Postmenopausal	8 634 (43.8)	8 671 (44.0)	–
Underwent hysterectomy and oophorectomy	2 754 (14.0)	2 713 (13.8)	–
Underwent hysterectomy	4 735 (24.0)	4 635 (23.5)	–
Underwent oophorectomy	132 (0.7)	121 (0.6)	–
Unknown	363 (1.8)	371 (1.9)	–
Level of education	(n = 18 935)	(n = 18 032)	
Grade 8	2 374 (12.5)	2 303 (12.8)	33.6
Grade 9–13	7 011 (37.0)	6 036 (33.5)	38.1
Trade or business school	6 662 (35.2)	6 650 (36.9)	18.9
University	2 888 (15.3)	3 043 (16.9)	9.4
Family history of breast cancer, family member	(n = 19 711)	(n = 19 694)	
Mother	1 489 (7.6)	1 522 (7.7)	–
Sister	1 258 (6.4)	1 242 (6.3)	–
Daughter	20 (0.1)	18 (0.1)	–
Second-degree relative‡	4 849 (24.6)	4 803 (24.4)	–
Place of birth	(n = 19 711)	(n = 19 694)	
North America	16 695 (84.7)	16 861 (85.6)	76.1
Europe	2 702 (13.7)	2 518 (12.8)	20.6
Elsewhere	284 (1.4)	275 (1.4)	3.3
Not available	30 (0.2)	40 (0.2)	–
Cigarette smoking status	(n = 19 711)	(n = 19 694)	
Never smoked	10 198 (51.7)	10 261 (52.1)	55.6
Smoked, no. of cigarettes			
1–10	1 470 (7.5)	1 411 (7.2)	8.6
11–20	1 689 (8.6)	1 734 (8.8)	12.8
> 20	1 290 (6.5)	1 260 (6.4)	10.6
Used to smoke	5 064 (25.7)	5 028 (25.5)	12.4
Occupation	(n = 18 323)	(n = 18 330)	
Not in workforce§	8 423 (46.0)	8 387 (45.8)	46.9
Clerical	3 672 (20.0)	3 660 (20.0)	16.6
Medical or health related	1 366 (7.5)	1 357 (7.4)	3.8
Teaching	918 (5.0)	925 (5.0)	3.0
Managerial or administrative	1 019 (5.6)	1 026 (5.6)	3.2
Science or technology related	411 (2.2)	443 (2.4)	1.2
Sales, service	1 723 (9.4)	1 736 (9.5)	15.9
Other	791 (4.3)	796 (4.3)	9.3

*MP = mammography and physical examination (PE) of the breasts, PO = physical examination of the breasts only.
†Single women not included for comparability with the Canadian population.
‡Includes aunts, cousins and other relatives.
§Includes women who were housewives, retired or unemployed.

tion of mammography decreased the interval cancer rate. The cumulative rate differed significantly between the two groups ($p < 0.0002$).

The denominator for the rate of incident cancer was the number of women in the same group who had not attended a screen for over 12 months (Table 5). The denominator for years 2 through 5 was the number of women who had not returned for screening at the visit before detection. Since one-third of the study population was eligible for four screens

Table 2: Frequency of referral to review clinic, by screen

Group; method by which abnormality detected	Screen; no. (and %) of women				
	1	2	3	4	5
MP group	(n = 19 711)	(n = 17 669)	(n = 17 347)	(n = 17 193)	(n = 9 876†)
Mammography (Ma) only	1 208 (6.1)	452 (2.6)	368 (2.1)	322 (1.9)	170 (1.7)
PE only	1 855 (9.4)	930 (5.3)	619 (3.6)	518 (3.0)	278 (2.8)
Ma and PE	309 (1.6)	71 (0.4)	57 (0.3)	34 (0.2)	27 (0.3)
All PE*	2 164 (11.0)	1 001 (5.7)	676 (3.9)	552 (3.2)	305 (3.1)
PO group	(n = 19 694)	(n = 17 453)	(n = 17 143)	(n = 16 918)	(n = 9 755†)
PE	2 207 (11.2)	1 032 (5.9)	710 (4.1)	642 (3.8)	366 (3.8)

*Number of women whose abnormality was detected by PE alone or in combination with Ma.
†Only 62% of the women were eligible for the fifth screen.

Table 3: Diagnostic procedures recommended* (R) and performed† (P) per 1000 women, by screen

Procedure; group	Screen									
	1		2		3		4		5	
	R	P	R	P	R	P	R	P	R	P
Fluid aspiration										
MP	12.2	7.8	5.9	4.4	4.4	3.3	3.4	2.7	1.9	2.2
PO	7.6	4.9	5.0	3.3	3.8	3.3	2.6	1.7	1.6	1.9
Tissue aspiration or needle biopsy										
MP	11.6	7.9	7.4	5.5	5.4	4.2	3.8	3.4	5.1	4.9
PO	9.7	7.6	7.1	5.4	4.2	3.2	3.4	2.8	4.1	2.9
Open surgical biopsy										
MP	24.9	24.8	10.6	10.4	6.9	7.0	6.0	5.8	5.3	5.5
PO	13.2	11.6	7.1	6.5	6.2	4.9	4.5	3.9	5.2	4.2
Needle localization biopsy										
MP	23.8	17.7	10.4	7.4	7.6	7.0	7.5	5.8	8.9	7.5
PO	0.5	0.6	0.5	0.3	0.2	0.0	0.2	0.2	0.9	0.4
Diagnostic Ma										
MP	1.0	4.2	0.5	1.8	0.4	1.2	0.3	0.8	0.2	0.8
PO	12.6	8.0	6.4	4.8	5.2	3.7	5.1	3.1	6.2	2.2

*Procedures recommended by an NBSS surgeon.
†Procedures performed in the community.

Table 4: Rates of biopsy detection of benign lesions per 1000 women, by screen

Screening method	Screen; biopsy rate									
	1		2		3		4		5	
	MP	PO	MP	PO	MP	PO	MP	PO	MP	PO
Ma only	24.3	–	8.9	–	6.7	–	5.7	–	7.1	–
PE only	5.4	8.7	3.9	5.0	2.9	3.7	2.3	2.9	1.9	2.7
Ma and PE	5.1	–	1.1	–	0.6	–	0.4	–	0.8	–
Overall rate	34.8	8.7	13.9	5.0	10.3	3.7	8.4	2.9	9.8	2.7
n	19 711	19 694	17 669	17 453	17 347	17 143	17 193	16 918	9 876	9 755

only, it became the denominator in the fifth year after entry. For women who entered the NBSS in 1984 and 1985 the data were probably incomplete at 6 and 7 years after entry; therefore, the rates of incident cancer for these years were not included in Table 5 (the numbers of women with breast cancer ascertained to date in these years were 30 in the MP group and 46 in the PO group).

The observed rates of invasive cancer for the 5 years after entry were compared with the expected rates (determined on the basis of data from Statistics Canada for 1980–86) (Table 6). Only cases of invasive cancer were included because cancer registries do not always include data for cases of in-situ cancer. The numerators were women with screen-detected, interval or incident invasive cancer. The denominators were women-years at risk. Year 1, the first 12-month period from the date of entry, included women whose cancer was detected at screen 1 and in interval 1. Year 2 included those whose cancer was detected at screen 2 or in interval 2 or was classified as incident 2. The cumulative rates for years 2 through 5 are at the bottom of Table 6. In the MP group the cumulative ratio of observed to expected rates of breast cancer (1.28) was statistically significant (95% confidence interval [CI] 1.05 to 1.56). In the PO group the ratio was 1.18 (95% CI 0.96 to 1.45).

Nodal status and tumour size of invasive cancers

At screen 1 more node-negative tumours and tumours with one to three nodes involved were detected in the MP group than in the PO group (Table 7); the difference was not statistically significant. At years 2 through 5 there were still more screen-detected node-negative tumours in the MP group, but there was little difference between the two groups in the number of node-positive tumours.

Table 7 also presents nodal status by mode of detection for screen-detected invasive cancers. At screen 1 the excess of tumours with no nodes or one to three nodes involved in the MP group was largely due to tumours found by mammography alone. For all screening years combined, 127 (47%) of the 268 invasive tumours in the MP group were detected by

Table 5: Detection rates of breast cancer, including in-situ cancer, per 1000 women, by year

Type of cancer; screening method	Year; detection rate									
	1		2		3		4		5	
	MP	PO	MP	PO	MP	PO	MP	PO	MP	PO
Screen-detected cancers										
Ma only	3.30	–	1.81	–	1.38	–	2.27	–	2.03	–
PE only	1.72	3.45	0.85	1.95	0.52	1.28	0.23	0.89	0.20	1.64
Ma and PE	2.18	–	1.08	–	0.58	–	0.64	–	0.61	–
Overall rate	7.20	3.45	3.74	1.95	2.48	1.28	3.14	0.89	2.84	1.64
n	19 711	19 694	17 669	17 453	17 347	17 143	17 193	16 918	9 876	9 755
Interval cancers										
Overall rate	0.76	0.81	0.57	0.92	0.46	1.52	0.52	0.95	0.51	1.64
n	19 711	19 694	17 669	17 453	17 347	17 143	17 193	16 918	9 876	9 755
Incident cancers										
Overall rate	–	–	3.28	1.90	1.96	3.89	1.44	2.87	0.78	1.25
n	–	–	1 832	2 101	2 041	2 312	2 088	2 435	19 159	19 273

Table 6: Observed and expected* incidence rates of invasive breast cancer and cumulative rates per 1000 women, by year

Year	MP group				PO group			
	No. of person-years	Observed rate	Expected rate	Ratio	No. of person-years	Observed rate	Expected rate	Ratio
1	19 529	135	37.3	3.6	19 587	82	37.4	2.2
2	19 416	66	38.5	1.7	19 498	53	38.6	1.4
3	19 334	47	39.7	1.2	19 409	47	39.8	1.2
4	19 220	53	40.8	1.3	19 328	41	41.0	1.0
5	19 127	39	42.0	0.9	19 239	49	42.2	1.2
Cumulative rates†		106.3	82.9	1.28		98.1	83.0	1.18
95% confidence interval (CI)				1.05–1.56				0.96–1.45

*Expected rates were based on data from Statistics Canada, 1980–1986.
†Rates for years 2 through 5.

mammography alone; 85 (67%) of them were node negative. Of the 141 detected by physical examination (alone or in combination with mammography) 88 (62%) were node negative. In the PO group 86 (58%) of the 148 invasive tumours were node negative.

At screen 1, 59 (50%) of the 119 tumours in the MP group and 22 (34%) of the 64 in the PO group were small (less than 20 mm in diameter). At screens 2 through 5 the corresponding figures were 102 (68%) of 149 and 39 (46%) of 84. Such tumours accounted for at least 36% of all incident or interval cancers in the two groups.

For all screening years combined, the MP group had significantly more small invasive tumours than the PO group if screen-detected, interval and incident tumours are combined (202 v. 144) and the PO group had more large tumours (20 mm or more) than the MP group (128 v. 104) ($p < 0.002$).

Mortality results

There were only a few differences between the two groups in the causes of death (Table 8). More women in the MP group than in the PO group died of pancreas cancer and hematopoietic neoplasms. The reverse was true for women who died of lung cancer and circulatory disease. None of these differences was statistically significant, however. The total number of deaths was almost equal in the two groups (253 in the MP group and 250 in the PO group).

Table 9 presents the number of deaths from breast cancer 7 years after entry according to the time and method of breast cancer detection. (Fewer deaths from breast cancer were recorded in Table 8 because the cutoff for the linkage with the Canadian Mortality Data Base, Statistics Canada, was Dec. 31, 1988.) More women in the MP group than in the PO group died of breast cancer detected at screen 1; the reverse was true for women who died of breast cancer detected in intervals 2 through 5. However, at 7 years the total number of deaths from breast cancer was virtually the same in the MP and PO groups (38 and 39 respectively). The ratio of the proportions of death from breast cancer in the MP group compared with those in the PO group was 0.97 (95% CI 0.62 to 1.52).

The lower part of Table 9 displays the cumulative observed rates and expected rates of death from breast cancer after 7 years of follow-up, but the ratios were not significantly higher than 1.

The survival rates from the time of entry were high in the two groups. At 7 years 91.2% of the

Table 7: Nodal status of all invasive tumours, by year*

Year; no. of nodes involved	Screen-detected cancer				Interval cancer		Incident cancer	
	MP			PO	MP	PO	MP	PO
	All	Ma alone	PE†					
Year 1								
None	75	32	43	37	6	6	–	–
1–3	22	8	14	11	4	4	–	–
≥ 4	9	0	9	11	1	4	–	–
Unknown	13	8	5	5	3	2	–	–
Total	119	48	71	64	14	16	–	–
Years 2–5								
None	98	53	45	49	17	42	10	26
1–3	28	12	16	21	6	13	2	4
≥ 4	12	5	7	11	4	5	4	2
Unknown	11	9	2	3	5	6	11	12
Total	149	79	70	84	32	66	27	44
Year 6 or more								
None	–	–	–	–	–	–	11	24
1–3	–	–	–	–	–	–	4	3
≥ 4	–	–	–	–	–	–	2	1
Unknown	–	–	–	–	–	–	12	18
Total	–	–	–	–	–	–	29	46
All years								
None	173	85	88	86	23	48	21	50
1–3	50	20	30	32	10	17	6	7
≥ 4	21	5	16	22	5	9	6	3
Unknown	24	17	7	8	8	8	23	30
Total	268	127	141	148	46	82	56	90

*For all dashes there was no cancer in this category by study design.
†Tumours detected at physical examination, alone or in combination with Ma.

women with invasive cancer in the MP group and 86.8% of those in the PO group were alive. Table 10 displays the survival rates from the date of diagnosis. The best survival was among women in the MP group with tumours detected at screens 2 through 5; the worst survival was among those in the PO group with interval cancer. The rates among women with tumours detected at screen 1 and those with incident cancer did not differ greatly between the two groups. In the MP group the women whose breast cancer had been detected by mammography alone had the highest survival rate.

Discussion

Study population and procedures

The NBSS is the only study reported to date evaluating the effect of mammography over and above physical examination among women aged 50

Table 8: Causes of death to end of 1988, by study group

Cause*	Group; no. (and %) of women: MP group	PO group
Cancer		
Breast	22 (8.7)	24 (9.6)
Colorectal	17 (6.7)	17 (6.8)
Hematopoietic	18 (7.1)	12 (4.8)
Lung	25 (9.9)	34 (13.6)
Ovarian	13 (5.1)	11 (4.4)
Other gynecologic	5 (2.0)	4 (1.6)
Pancreas	13 (5.1)	5 (2.0)
Stomach	7 (2.8)	3 (1.2)
Other	33 (13.0)	35 (14.0)
Central nervous system disorder (nonvascular)	6 (2.4)	4 (1.6)
Circulatory disorder	46 (18.2)	54 (21.6)
Endocrine or metabolic condition	5 (2.0)	5 (2.0)
External cause (violent)	24 (9.5)	26 (10.4)
Infection or parasitic disease	2 (0.8)	0
Respiratory disease	5 (2.0)	3 (1.2)
Miscellaneous	12 (4.7)	12 (4.8)
Unknown	0	1 (0.4)
Total	253	250

*The tabulated underlying cause of death was calculated on the basis of all available information.

Table 9: Cumulative number of deaths from breast cancer 7 years after entry, by study group and time of breast cancer detection

Time of detection	Group; no. of deaths: MP	PO
Screen 1	18	8
Screens 2–5	10	9
Interval 1	5	5
Intervals 2–5	2	13
Incident (> 12 mo after last screen)		
Among noncompliers	2	2
After scheduled end of screening	1	2
Total	38	39
Cumulative rates*		
Observed	18.4	19.0
Expected	19.8	19.8
Ratio	0.93	0.96
95% CI	0.55–1.48	0.57–1.51

*Rates are per 10 000 person-years.

to 59 years. Other studies have compared screening with no screening.

All of the participants were well matched by group. As in the accompanying paper we concluded that randomization bias did not occur, because the relevant risk factors and the number of women referred to the review clinic were equally distributed between the two groups.

The participants differed in several important respects from the Canadian population. In particular, they had a higher socioeconomic status. This and other analyses[13-15] have shown that the participants had, if anything, more risk factors for breast cancer; therefore, their expected incidence rate of breast cancer should be at least as great as the rate in the Canadian population.

Cancer detection

The cancer detection rates in the MP group (Table 5) correspond to those reported from previous studies.[16,17] The rates were higher in the MP group than in the PO group throughout screening. These rates were achieved at the cost of high rates of benign biopsy results, a finding similar to the US experience.[12] The ratios of benign to malignant lesions were higher than those reported from European studies,[18,19] in which the diagnostic procedures had been controlled by the screening centre.

Previous studies have not yielded the cancer detection rates to be expected from physical examination only. Although detection rates have been published for physical examination alone from the UK Trial of Early Detection of Breast Cancer[20] these cannot be compared with our rates in the PO group (Table 5), because in the UK study women aged 45 to 64 years on entry were included and, more important, the physical examinations followed screening in which mammography had been performed a year before, so that cancers detected by mammography would not have been "available" for detection by physical examination the next year.

As pointed out in the accompanying paper our rates of interval cancer cannot be directly compared with those from other studies that involved women with negative findings at the previous screen. Furthermore, all of our participants were taught and urged to practise breast self-examination, which led to the detection of cancer in some cases, thus potentially reducing the delay in diagnosis. Even so, the use of mammography reduced the rates of interval cancer in the MP group, and the survival rate among women in the PO group with interval cancer was the lowest.

Table 10: Survival rates among women with breast cancer from date of diagnosis, by detection category and group

Year from diagnosis	Screen 1		Screens 2–5		All screen-detected cancers			
					MP			
	MP	PO	MP	PO	Ma alone	PE alone	Ma + PE	PO
1	100.0	100.0	100.0	97.7	100.0	100.0	100.0	98.7
2	100.0	97.1	99.0	96.6	100.0	98.4	98.9	96.8
3	97.9	95.6	96.8	93.1	99.4	90.6	97.8	94.2
4	95.8	94.1	95.7	91.9	97.6	90.6	95.5	92.8
5	94.4	94.1	95.0	91.9	96.3	90.6	94.2	92.8
6	90.8	92.6	95.0	87.9	93.7	88.8	92.7	90.2
7	87.4	87.3	95.0	87.9	92.5	88.8	86.3	86.7
No. of cancers	142	68	191	87	180	64	89	155
No. (and %) of deaths	17 (12.0)	8 (11.8)	9 (4.7)	9 (10.3)	10 (5.6)	7 (10.9)	9 (10.1)	17 (11.0)

Year from diagnosis	Interval cancers		Incident cancers	
	MP	PO	MP	PO
1	100.0	100.0	100.0	100.0
2	97.8	96.2	93.9	95.1
3	95.5	90.6	90.2	92.1
4	90.9	87.7	90.2	92.1
5	88.4	80.0	90.2	92.1
6	85.6	78.2	90.2	92.1
7	82.1	73.2	90.2	92.1
No. of cancers	47	88	58	90
No. (and %) of deaths	7 (14.9)	17 (19.3)	3 (5.2)	3 (3.3)

The substantial excess of node-negative and small tumours in the MP group resulted from the addition of mammography to screening with physical examination. Yet, with up to 7 years of follow-up from entry, this addition did not reduce the cumulative incidence rate of node-positive breast cancer, although there was a small reduction in the number of large tumours. The estimated sensitivity and specificity of the NBSS screening methods,[6-8] the objective demonstration that the technical quality of mammography improved over time[17,21] and the observed cancer detection rates all confirm that the NBSS met appropriate standards.

Rates of death and survival

The death rates were compatible with the cancer detection rates in that similar numbers of advanced tumours in the two groups were parallelled by similar numbers of deaths from breast cancer. The use of mammography achieved the expected cancer detection rates, but the only survival advantage was for the women with breast cancer detected by mammography alone. So far a reduction in the death rate has not followed, presumably because the increase in the survival rate was largely attributable to lead time. That lead time was gained even among women who died of breast cancer is evident in that 18 (47%) of the 38 women who died in the MP group had tumours detected at screen 1, as compared with only 8 (20%) of the 39 women who died in the PO group ($p < 0.013$) (Table 9). The "deficit" in deaths in the PO group is made up by women who had tumours detected at intervals 2 through 5. Thus, the use of mammography advanced the time of detection by at least a year for about a quarter of the women who died of breast cancer in the MP group.

The NBSS comparison of mammography plus physical examination with physical examination alone is unique. Most studies have shown that women aged 50 years or more benefit early from combined screening[22,23] or from mammography alone.[24-27] Even so, two reports of combined screening[20,28] and one of mammography alone[29] showed no evidence of effectiveness overall, although in at least two of them[20,29] a reduction in the rate of death from breast cancer similar to that seen in other studies[22,25] occurred 5 or more years after the start of screening.

One potential bias that might have influenced our results must be considered. The number of deaths recorded since 1988, from follow-up of the participants and cancer registry linkages, may not represent all of the women who died of breast cancer. Nevertheless, the numbers were similar in the two groups (16 in the MP group and 15 in the PO group). Given the almost complete absence of death from breast cancer in the first 2 years after diagnosis, cancer diagnosed after the registry linkage cutoff dates would probably not result in many deaths. Thus, it seems unlikely that many deaths were missed or that the missed deaths would markedly change the observed distribution of deaths from breast cancer.

Although screening with mammography increased the cancer detection rates it did not, when added to skilled physical examination of the breasts, reduce the rate of death from breast cancer in the first 7 years after entry. The high survival rate among most women with breast cancer, at least in the first 5 years after diagnosis, means that the potential for mammography screening to lower the death rate by 40% in the short term is reduced. The NBSS was designed with sufficient power to detect a reduction of 40% in the death rate, not 30% or less. If the real benefit of mammography plus physical examination and breast self-examination is a reduction of 30% or less, this can be revealed only through further follow-up to permit a sufficient number of deaths from breast cancer to occur. Follow-up of the participants continues, and we plan to report the 10-year results in about 3 years.

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References

1. Miller AB, Howe GR, Wall C: The National Study of Breast Cancer Screening: protocol for a Canadian randomized controlled trial of screening for breast cancer in women. *Clin Invest Med* 1981; 4: 227-258
2. Day NE, Baines CJ, Chamberlain J et al: UICC project on screening for cancer: report of the workshop on screening for breast cancer. *Int J Cancer* 1986; 38: 303-308
3. Report of the Working Group to Review the National Cancer Institute-American Cancer Society Breast Cancer Detection Demonstration Projects. *J Natl Cancer Inst* 1979; 62: 639-709
4. Baines CJ: Impediments to recruitment in the Canadian National Breast Screening Study: response and resolution. *Controlled Clin Trials* 1984; 5: 129-140
5. Baines CJ, To T: Changes in breast self-examination behavior achieved by 89,835 participants in the Canadian National Breast Screening Study. *Cancer* 1990; 66: 570-576
6. Baines CJ, Wall C, Miller AB et al: Sensitivity and specificity for first screen mammography in a Canadian national breast screening study. *Radiology* 1986; 160: 295-298
7. Baines CJ, McFarlane DV, Miller AB et al: Sensitivity and specificity of first screen mammography in 15 NBSS centres. *J Can Assoc Radiol* 1988; 39: 273-276
8. Baines CJ, Miller AB, Bassett AA et al: Physical examination: evaluation of its role as a single screening modality in the Canadian National Breast Screening Study. *Cancer* 1989; 63: 160-166
9. Miller AB: The Canadian National Breast Screening Study. In Day NE, Miller AB (eds): *Screening for Breast Cancer*, Huber, Toronto, 1988: 51-58
10. Miller AB, Baines CJ, To T et al: The Canadian National Breast Screening Study. In Miller AB, Chamberlain J, Day NE et al (eds): *Cancer Screening*, Cambridge U Pr, Cambridge, Engl, 1991: 45-55
11. *1981 Census of Canada* (public use sample tape 8-1200-609), Statistics Canada, Ottawa
12. McLelland R, Pisano ED: The politics of mammography. *Radiol Clin North Am* 1992; 30: 235-241
13. Schechter MT, Miller AB, Baines CJ et al: Selection of women at high risk of breast cancer for initial screening. *J Chronic Dis* 1986; 39: 253-260
14. Holowaty PH, Miller AB, Baines CJ et al: Risk factors for breast cancer occurring after an initial screen in the Canadian National Breast Screening Study. *Cancer Epidemiol Biomarkers Prevent* (in press)
15. Simard A, Paquette L, Baillargeon J et al: Perception of cancer detection and early treatment in a population participating in the National Breast Screening Study in Canada. *Can J Public Health* 1989; 80: 226-227
16. Baker LH: Breast Cancer Detection Demonstration Project: five-year summary report. *CA Cancer J Clin* 1982; 32: 194-225
17. Miller AB, Baines CJ, Sickles EA: Canadian National Breast Screening Study [C]. *AJR* 1990; 155: 1133-1134
18. Tabár L, Akerlund E, Gad A: Five-year experience with single-view mammography randomized controlled trial in Sweden. *Recent Results Cancer Res* 1984; 90: 105-113
19. United Kingdom Trial of Early Detection of Breast Cancer Group: Specificity of screening in United Kingdom Trial of Early Detection of Breast Cancer. *BMJ* 1992; 304: 346-349
20. UK Trial of Early Detection of Breast Cancer Group: First results on mortality reduction in the UK Trial of Early Detection of Breast Cancer. *Lancet* 1988; 2: 411-416
21. Baines CJ, Miller AB, Kopans DB et al: Canadian National Breast Screening Study: assessment of technical quality by external review. *AJR* 1990; 155: 743-747
22. Shapiro S, Strax P, Venet L: Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA* 1971; 215: 1777-1785
23. Collette HJA, Day NE, Rombach JJ et al: Evaluation of screening for breast cancer in a non-randomised study (the Dom project) by means of a case-control study. *Lancet* 1984; 1: 1224-1226
24. Verbeek ALM, Hendriks JHCL, Holland R et al: Mammographic screening and breast cancer mortality: age-specific effects in Nijmegen Project, 1975-82 [C]. *Lancet* 1985; 1: 865-866
25. Tabár L, Fagerberg CJG, Gad A et al: Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985; 1: 829-832
26. Frisell J, Eklund G, Hellström L et al: Randomized study of mammographic screening — preliminary report on mortality in the Stockholm trial. *Breast Cancer Res Treat* 1991; 18: 49-56
27. Palli D, del Turco R, Buiatti E et al: A case-control study of the efficacy of a non-randomized breast cancer screening program in Florence (Italy). *Int J Cancer* 1986; 38: 501-504
28. Roberts MM, Alexander FE, Anderson TJ et al: Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990; 335: 241-246
29. Andersson I, Aspegren K, Janzon L et al: Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *BMJ* 1988; 297: 943-948

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